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EXAMINER	
DO, PENSEE T	

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1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/813,444	IVERSON ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12,15 and 18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12,15 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application 09813444, PG Pub. No. 20040072740 filed 03/20/2001 is a continuation of 08847063, filed 05/01/1997 ,now abandoned. Application 08847063 is a continuation in part of 08447402, filed 05/23/1995 ,now U.S. Patent #5866344. Application 08447402 is a continuation in part of 08258543, filed 06/10/1994 ,now abandoned. Application 08258543 is a division of 07794731, filed 11/15/1991 ,now U.S. Patent #5348867.

The effective filing date of this application is 3/20/2001. Although this application is a continuation of application 08847063, application 08/847,063 just merely mentions that yeast is one of the host cells. Application 08/847,063 fails to describe or support for a method of selecting yeast host cell that expresses a desired antibody or fragment thereof. All the examples in 08/847,063 are drawn to expressing antibody/fragments in E. coli. which is very different from yeast?

Information Disclosure Statement

The IDS submitted on May 17, 2010 is acknowledged and considered.

Amendment Entry & Claims Status

The amendment filed on April 13, 2010 has been acknowledged and entered.

Claims 1, 6-12, 15, 18-26 are pending and being examined.

Claims 2-5, 13-14, 16-17, 27-46 are cancelled.

Withdrawn Rejection(s)

Rejections under 102 and 103 in the previous office action are withdrawn herein.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6-12, 15, 18-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Georgiou et al. (US 5,866,344).

Georgiou teaches a method of selecting a polypeptide, i.e. antibody, from a plurality of candidate proteins comprising the steps of : obtaining a library of vectors that encode a plurality of distinct candidate polypeptides; wherein the vector provides for the cell surface expression of said candidate polypeptides; expressing each of said plurality

of candidate polypeptides on the surface of a host cell; and selecting a host cell that expresses a desired polypeptides. (see col. 3, line 65-co1.4, line 40). Expression libraries are prepared such that an expressed protein is displayed on the surface of the cell. Typically the po!ypeptides will be surface expressed in a host cell such as bacterial, yeast, insect, eukaryotic or mammalian cells. Surface expression of a polypeptide, e.g. antibody, on a cell surface is achieved using a recombinant vector that promotes display on the outer membrane of a host cell. (see col. 4, lines 9-21). Vectors appropriate for a bacterial host cell include at least three DNA segments as part of a chimeric gene.

For claims 6-9, and 18, Georgiou teaches screening for antibodies allows one to select an antibody or antibody fragment from a plurality of candidate antibodies that have been expressed on the surface of a host cell. Once an antibody expression library is prepared, the selected antigen for which one desires to identify and isolate specific antibody or antibodies is labeled with a detectable label, i.e. fluorescent label. (see col. 5, line 40-col. 6, line 3).

For claim 10, Georgiou teaches that the cells are sorted using FACS which includes size sorting. (see col. 6, lines 6-10).

For claims 11 and 12, Georgiou teaches the antibodies are obtained from an expressing vector library that may be prepared from DNAs encoding antibodies or antibody fragments. One source of such DNAs could be from an animal immunized with a selected antigen; or antibody genes from other sources such as those produced by hybridomas or produced by mutagenesis of a known antibody gene. One preferred

method of obtaining DNA segments is to isolate mRNA from antibody cells of an immunized animal. The mRNA may be amplified and used to prepare DNA segments to include in the vectors. One may also employ DNA segments that have mutagenized from one or more DNAs that encode a selected antibody or antibody fragment. Once an antibody expression library is prepared, the selected antigen for which one desires to identify and isolate specific antibody or antibodies is labeled with a detectable label. (see col. 4, lines 23-40; col. 5, lines 44-58).

For claim 15, Georgiou teaches the selected cells that express a desired antibody are subjected to cleavage to release the selected antibody or antibody fragment from the surface of the outer membrane by adding a protease. (See example 3).

For claim 19, Georgiou teaches the cells that bind to the selected antigen are identified by contacting said plurality of cells with detectably labeled antigen under conditions effective to allow antibody-antigen binding; removing non-specifically bound antigen from cells; and identifying the antibody- or antibody fragment-expressing cells by detecting the presence of the label. (See col. 12, lines 14-21).

For claim 20, cell surface displayed antibodies may be rapidly and efficiently sorted using fluorescent activated cell sorting techniques (FACS) (see col. 11, lines 45-50).

For claims 21-23, Georgiou teaches the cells are subjected to a first and a second round of automated cell sorting and regrowth of sorted cells is conducted between the two rounds of cell sorting. (see col. 25, lines 49-56).

Claims 1, 6-12, 15, 18-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Kieke et al. (US 6,300,065 filed on August 26, 1998, with a provisional filing date of May 31, 1996- provisional discussed surface expression of antibodies on yeast cells).

Kieke teaches a method for selecting proteins with enhanced phenotypic properties relative to those of a wild-type of said protein, comprising the steps of:

transforming yeast cells with a vector expressing a protein to be tested fused to a yeast cell wall protein, wherein mutagenesis is used to a generate a variegated population of mutants of the protein to be tested;

contacting said yeast cells with a first label, wherein said first label associates with yeast expressing said protein having enhanced phenotypic properties and does not associate with yeast which do not express said protein having enhanced phenotypic properties;

isolating said yeast cells with which said first label is associated;

analyzing and comparing said phenotypic properties of said mutant protein expressed by yeast with phenotypic properties of said wild-type protein; and

selecting yeast cells exhibiting mutant proteins with enhanced phenotypic

properties over the wild-type protein; where enhanced phenotypic properties are one or more of surface expression level, stability, secretion levels and solubility. (see col. 4, lines 45-58).

For claims 6-9, 18-20, the protein/antibody fragment on the cell surface of yeast is contacted with an antigen labeled with fluorescein. (see col. 4, lines 37-44). The yeast host cells are subjected to automated cell sorting using FACS (flow cytometry cell sorting) (see col. 6, lines 43-57) to identify the host cell that expresses the antibody/fragment by detecting the fluorescently labeled sorted cells.

For claim 10, the cells are subjected to size sorting via FACS (see col. 6, lines 43-57).

For claims 21-24, Kieke teaches sorting the cells in a first round, regrowing the cells, sorting them in a second, third and fourth rounds. (see example 5).

For claims 25-26, Kieke teaches using magnetic bead as label and the cells are subjected to magnetic sorting. (see claim 8).

Claims 1, 6-9, 18-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Higuchi et al. (US 6,214,613).

Higuchi teaches a method for selecting a eukaryotic host cell that expresses a desired antibody or antibody fragments from a plurality of host cells expressing candidate antibodies or antibody fragments, the method comprising: obtaining a vector

that has different sequences, one sequence coding is for H-chain variable regions of antibodies and another sequence coding for L-chain variable regions of antibodies. The vector provides cell surface expression of candidate antibodies or fragments. (see col. 3, line 10-col. 4, line 21). Antibodies expressed on the membrane of the host cells are secretory type and membrane bound type. The constant region of eh antibodies was made in secretory type for possible expression of the antibodies, and the transmembrane domain of the membrane protein other than antibody is linked to carboxyl terminus of H-chain and/or L-chain of the antibodies for expressing the antibodies on the cell membrane. In case that any one of a nucleotide sequence of AKL and AKH is integrated in the vector, the chain, which is not integrated therein is previously incorporated in the host cells, or should be incorporated in the host cells by co-transduction of the other vector containing the chain. (see col. 5, lines 35-55). Thus, Higuchi teaches a plurality of vectors being incorporated into the host cells. The vectors express different types of antibodies such as secretory antibodies and membrane bound antibodies. (see col. 5, lines 35-45). Since Higuchi teaches that host cells are eukaryotic cells, it is inherent that eukaryotic cells encompass yeast, mold, algae or insect cells.

For claims 6 and 9, Higuchi teaches a method of selecting a host cell that expresses a desired antibody comprises the steps of contacting the antibody/fragment expressing cells with a selected antigen; and identifying the host cell that binds to said selected antigen. (see col. 7, lines 35-48).

For claims 7, 8, and 18 the antigen is labeled with fluorescent. (see col. 5, lines 47-48).

Regarding claim 19, Higuchi teaches the method of selecting antibody expressing cells by contacting the cells with labeled antigens to allow specific antigen-antibody binding and removing non-binding cells by washing; and detecting the labels of the bound cells. (see col. 12, lines 35-45).

Regarding claims 20 and 21, automated cell sorting is by flow cytometry. (see col. 12, lines 46-50).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 24 is rejected under U.S.C. 103(a) as being unpatentable over Georgiou in view of Boder et al. (Nature Biotechnology Volume 15 June 1997, pp. 553-557).

Georgiou has been discussed above.

However, Georgiou fails to teach performing a third and fourth rounds of automated cell sorting.

Boder teaches samples of cells were sorted using flow cytometry. The collected cells were regrown in glucose medium prior to repeating the sorting. A total of four

rounds of sorting and amplification were performed to provide a high recovery of all positive clones. (see p. 557, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to apply the method of Boder to sort cells, regrow, repeating sorting for several rounds when selecting host cells in the method of Georgiou to ensure a high recovery of all positive clones/cells containing the target polypeptides/antibodies/fragments.

Claims 25 and 26 are rejected under U.S.C. 103(a) as being unpatentable over Georgiou in view of Slamon (US 4,918,162).

Georgiou has been discussed above.

However, Georgiou fails to teach using magnetic bead linked to the antigen;

Slamon teaches selecting a host cell that expresses the desired polypeptides comprises the steps of contacting said antibody or antibody-fragment-expressing cells with a selected antigen; and identifying a host cell that binds to said selected antigen (see col. 9, line 23-col. 10, line 14). The antigen/polypeptide is labeled with a fluorescers, chemiluminescers, magnetic particles etc. (see col. 6, lines 58-68).

Since it is well known in the art magnetic bead can be as label conjugated to antigen to screen expressed antibodies on cell surface as taught by Slamon, it would also have been prima facie obvious to one of ordinary skill in the art to use magnetic beads coupled to antigen as taught by Slamon for detecting antibodies expressed in host cells as taught by Georgiou since Slamon teaches that magnetic beads are capable of coupling to antigen and usable as labels for detecting antibodies. Magnetic

beads advantageous as carriers or labels for separation and detection of antibodies in general. It is also well known that manipulation of magnetic particles require a magnetic field.

Claims 11, 15 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi or Kieke in view of Slamon (US 4,918,162).

Higuchi and Kieke have been discussed above.

However, Higuchi and Kieke fail to teach a method of obtaining a vector library by administering to an animal an antigen; obtaining from the animal a plurality of distinct DNA segments that encode distinct antibodies or fragments; and incorporating said plurality of DNA segments into a plurality of vectors; the vectors expressing antibodies on the outer membrane surface of a host cell; and Higuchi fails to teach using magnetic bead linked to the antigen; subjecting the expressed antibody to cleavage to release the antibody from the surface of the outer membrane.

Slamon teaches methods for identifying and monitoring human cancers. The methods rely on the detection of N-myc protein in a biological specimen, usually a cell sample such as tissue sample or sputum sample. Presence of the N-myc protein in the biological specimen may be diagnostic and/or prognostic of the cancer. Polypeptides and antibodies are used for detecting the N-myc proteins, where the polypeptides are associated with immunogenic sites on the protein. The polypeptides may be natural or synthetic. Such polypeptides include the N-myc protein in substantially pure form as well as fragments thereof. Monoclonal or polyclonal antibodies against the polypeptides

are prepared by conventional techniques. Six polypeptides capable of eliciting antibodies useful in the present method have been identified. The method of synthesizing the polypeptides involves the expression in cultured cells of recombinant DNA molecules encoding a desired portion of the N-myc gene. Suitable cDNA and genomic libraries may be obtained from human cell lines known to contain the N-myc gene. (see col. 1, line 65-col. 2, line 48; col. 4, lines 36-49). The natural or synthetic DNA fragments coding for a desired N-myc fragment will be incorporated in DNA constructs capable of introduction to and expression in an in vitro cell culture. Usually, the DNA constructs will be suitable for replication in a unicellular host, such as yeast or bacteria i.e. negative bacteria E.coli. but may also be intended for introduction and integration within the genome of cultured mammalian or other eukaryotic cell lines. DNA constructs prepared for introduction into bacteria or yeast will include a replication system recognized by the host. Available expression vectors, which include the replication system and transcriptional and translational regulatory sequences together with an insertion site for the N-myc DNA sequence may be employed. (see col. 4,lines 62-68; col. 5, lines 1-15; col. 9, lines 65-66). The polypeptide can be an antibody or antibody fragment. The step of selecting a host cell that expresses the desired polypeptides comprises the steps of contacting said antibody or antibody-fragment-expressing cells with a selected antigen; and identifying a host cell that binds to said selected antigen (see col. 9, line 23-col. 10, line 14). The antigen/polypeptide is labeled with a fluorescers, chemiluminescers, magnetic particles etc. (see col. 6, lines 58-68). The natural or synthetic DNA fragments coding for a desired N-myc fragment will be

incorporated into DNA constructs capable of introduction and expression in cell culture. DNA constructs are suitable for replication in unicellular host such as yeast or bacteria, but may be used with mammalian or other eukaryotic cell lines. (see col. 4, line 63-col. 4, line 1). The vector library is obtained by administering to an animal such as a mouse a desired antigen. The mouse is then killed, the spleen removed, and the spleen cells immortalized. DNA segments that encode distinct antibodies or antibody fragments were obtained and incorporated into a plurality of expression vectors, the vectors expressing antibodies or antibody fragments on the outer membrane surface of a Gram negative host cell, E. coli. (see col. 4, lines 62-68; col. 5, line 1-68). Selected cells that express a desired antibody are subjected to cleavage to release the selected antibody or antibody fragment from the surface of the outer membrane. (see col. 7, lines 27-50).

It would have been prima facie obvious to one of ordinary skill in the art to use the general method of obtaining a vector library of Slamon to obtain a vector library for use in the method of Higuchi or Kieke since they all teach using vectors to express desired antibodies/fragments in host cells to the advantage that immortalized cell lines are capable of producing antibodies having a desired specificity. It is advantageous to use monoclonal antibodies because they are highly specific.

For claim 15, since Higuchi or Kieke teaches the antibodies expressed in host cell of their invention are secretory type or membrane-bound type and Slamon teaches releasing the selected antibody from the surface of the outer membrane, it would have been prima facie obvious to one of ordinary skill in the art to use cleave the secretory type antibodies of Higuchi in order to detect these secretory antibodies effectively and it

is advantageous to cleave these secretory antibodies from cell membrane to distinguish from the membrane-bound antibodies.

For claims 25, 26, it would also have been prima facie obvious to one of ordinary skill in the art to use magnetic beads coupled to antigen as taught by Slamon for detecting antibodies expressed in host cells as taught by Higuchi since Slamon teaches that magnetic beads are capable of coupling to antigen and usable as labels for detecting antibodies. Magnetic beads advantageous as carriers or labels for separation and detection of antibodies in general. It is also well known that manipulation of magnetic particles require a magnetic field.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi or Kieke in view of Sharon (US 5,789,208 filed February 19, 1997).

Higuchi and Kieke have been discussed above.

However, Higuchi and Kieke fail to teach obtaining a plurality of DNA segments by the method comprising isolating mRNA from antibody-producing cells of an animal; amplifying a plurality of distinct DNA segments using a set of nucleic acid primers having sequences complementary to antibody constant region or antibody framework region nucleic acid sequences and preparing a plurality of distinct DNA segments having sequences complementary to said amplified RNA segments.

Sharon teaches the vector library is obtained by administering to an animal an effective amount of selected antigen; the V_H and V_L mRNA of the animal are reverse

transcribed into V_H and V_L cDNA sequences which are PCR amplified with the resulting amplified sequences linked. The linked sequences are PCR amplified to create a population of DNA fragments which encode V_H and V_L antibody fragments that are cloned into expression vectors and the population of cloned expression vectors expanded. The expression vectors which encode antigen- or tissue-specific antibodies or fragments thereof may be selected and the subpopulation selected expanded to produce a library. (see col. 16, line 56-col. 17, line 20).

Since it is well known in the art as taught by Sharon that the DNA segments that are incorporated into the expression vector must be prepared and Higuchi teaches incorporating a plurality of DNA segments into expression vectors to express antibodies on the surface of a host cell, it would have been prima facie obvious to one of ordinary skill in the art to isolate those DNA segments as taught by Sharon so that DNA segments encoding the antibodies/fragments of interest can be expressed on the host cell.

Claims 10, 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi in view of Boder et al. (Nature Biotechnology Volume 15 June 1997, pp. 553-557).

Higuchi has been discussed above.

However, Higuchi fails to teach sorting the cell by size; and sorting the cell for a second round; regrowth the sorted cells and sorting them for a third and fourth round.

Boder teaches samples of cells were sorted using flow cytometry. The collected cells were regrown in glucose medium prior to repeating the sorting. A total of four rounds of sorting and amplification were performed to provide a high recovery of all positive clones. (see p. 557, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to apply the method of Boder to sort cells, regrow, repeating sorting for several rounds when selecting host cells in the method of Higuchi to ensure a high recovery of all positive clones/cells containing the target polypeptides/antibodies/fragments.

Claims 1, 6, 9, 11, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharon (US 5,789,208 filed February 19, 1997) in view of Boder et al. (Nature Biotechnology Volume 15 June 1997, pp. 553-557).

Sharon teaches a method of obtaining a library of vectors that encode a plurality of distinct candidate of polyclonal antibodies or antibody fragments (see col. 13, lines 34-40), wherein said vector provides for cell surface expression of said candidate polyclonal antibodies (see col. 14, lines 33-37); expressing each of the antibodies or fragments thereof on a phage surface (col. 13, lines 34-46) that expresses a desired polyclonal antibody or fragment thereof (see col. 14, lines 33-37).

However, Sharon fails to teach expressing the antibodies or fragments thereof on the surface of a yeast cell.

Boder teaches expressing antibodies or fragments thereof on a yeast cell since yeast cell possesses protein folding and secretory machinery strikingly homologous to that of mammalian cells. Yeast also is an easy cultured single-cell microbe with facile genetics and is better suited for library methods than cultured mammalian cells. Thus, a eukaryotic display system using Yeast as a host organism should alleviate library biases towards soluble expression in E. coli /phage while retaining the benefits of large numbers of displayed fusions per cell and flow cytometric screening capable of precise quantitative discrimination. (see entire document especially pg. 563).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to express the library of antibodies or fragments thereof taught by Sharon on yeast surface as taught by Boder since yeast is an easy cultured single-cell microbe with facile genetics and is better suited for library methods than culture mammalian cells and yeast also has protein folding homologous to that of mammalian cells. Furthermore, compared to phage surface expression, yeast alleviates biases toward soluble expression while retaining the benefits of large numbers of displayed fusion per cell. (see Boder entire document especially pg. 563). One of ordinary skills in the art would have a reasonable expectation of success in combining these teachings since both teach displaying library of antibodies or fragments thereof in host cell such as yeast.

For claims 6 and 9, Boder teaches that the antibody fragment scFv displayed on the yeast surface specifically binds antigens. Thus, the scFv must be contacted with antigen and yeast host cell that expresses such scFv is identified. (see Boder p. 556, first column, last paragraph).

For claims 11 and 12, Sharon teaches the vector library is obtained by administering to an animal an effective amount of selected antigen; the V_H and V_L mRNA of the animal are reverse transcribed into V_H and V_L cDNA sequences which are PCR amplified with the resulting amplified sequences linked. The linked sequences are PCR amplified to create a population of DNA fragments which encode V_H and V_L antibody fragments that are cloned into expression vectors and the population of cloned expression vectors expanded. The expression vectors which encode antigen- or tissue-specific antibodies or fragments thereof may be selected and the subpopulation selected expanded to produce a library. (see col. 16, line 56-col. 17, line 20).

Claims 7, 8, 18, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharon in view of Boder et al. as applied to claim 1 above, and further in view of Yokoyama (US 5,646,011).

Sharon and Boder have been discussed above.

However, they fail to teach labeling the antigen with a fluorescent label.

Yokoyama teaches a method of identifying tumor cells by contacting a sample of tumor cells with a molecule which binds to the protein isolated. Such molecule is labeled with a fluorescent marker, radioactive isotope or enzyme. (see col. 3, lines 50-60). The protein is isolated by incorporated the nucleic acids into a recombinant expression vector which ensures good expression of the nucleic acids in a host cell. (see col. 10,

lines 50-55). The host cells are prokaryotic or eukaryotic cells such as insect cells, yeast, or mammalian cells. (see col. 11, lines 10-15).

It would have been prima facie obvious to one of ordinary skill in the art to label the antigen instead of the antibody as in Sharon and Boder according to the method of Yokoyama since it is well known that the label can be either on the target or the binding partner of the target.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sharon in view of Boder et al. as applied to claim 1 above, and further in view of Slamon (US 4,918,162).

Sharon and Boder have been discussed above.

However, they fail to teach cleaving the antibody from the cell membrane.

Slamon teaches selected host cells that express a desired antibody are subjected to cleavage to release the selected antibody or antibody fragment from the surface of the outer membrane. (see col. 7, lines 27-50).

Since Sharon and Boder teach that the antibodies expressed in host cell of their inventions are membrane-bound type and Slamon teaches releasing the selected antibody from the surface of the outer membrane, it would have been prima facie obvious to one of ordinary skill in the art to cleave the antibodies obtained by the method of Sharon modified by Boder for further analysis of the membrane antibodies or for therapeutic purposes. One of ordinary skill in the art would have a reasonable

expectation of success in combining these teachings because they all teach expressing antibodies/fragments on the surface of cells.

Claims 10, 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharon in view of Boder as applied to claim 1 above, and further in view of Civin (US 5,081,030 submitted by Applicants on IDS 3/10/05).

Sharon and Boder have been discussed above.

However, they fail to teach cell separation techniques such as fluorescently-activated cell sorting/flow cytometry or magnetic separation; and subjecting cells to multiple rounds of sorting by flow cytometry.

Civin teaches well known cell sorting techniques such as fluorescently-activated cell sorting/flow cytometry or magnetic separation for cell surface ligands. (See col. 4, line 14-54).

It would have been prima facie obvious to one of ordinary skill in the art to use cell sorting techniques described by Civin to sort cells that comprises surface antibodies produced by the method of Sharon modified by Boder since these techniques are well known and cell sorting is necessary to obtain the host cells that contain the antibodies produced by the method of Sharon modified by Boder. Regarding the multiple rounds of flow cytometry, it would have been obvious to one of ordinary skills in the art to subject the host cells to multiple rounds of cell sorting using flow cytometry to obtain a highly purified cell population that contain the target antibodies.

Response to Arguments

Applicant's arguments with respect to claims 1, 6-12, 15, 18-26 have been considered but are moot in view of the new ground(s) of rejection.

Applicants argue that Sharon fails to teach at least three elements:

1/. Sharon fails to teach expressing antibodies/fragments on yeast cells. Instead, Sharon teaches expressing antibodies on phage surface.

2/. Sharon fails to teach selecting yeast host cell that expresses a desired antibody/fragment on its surface.

3/. Sharon fails to teach contacting the yeast host cell that expresses the antibody/fragment on its surface with an antigen. Rather, Sharon teaches contacting antigen-stimulated cells to generate an antibody producing hybridomas.

The arguments are found persuasive. Therefore, the rejections in the previous office action are withdrawn.

However, the new reference, Boder, teaches the above missing elements in Sharon.

Regarding the effective filing date, after a close review of the parent application, 08847063, filed 05/01/1997, it is found that the parent application just merely mentions yeast is one of host cells and the whole invention, including the examples, revolves around using E. coli as host cell for surface expressing of antibodies/fragments. Therefore, the effective filing date of this application is its filing date which is March 20, 2001.

Higuchi (6,214, 613), which was previously applied in the non-final office actions sent 3/10/2005 and 10/23/2006, is now re-applied since Higuchi has an earlier date than the effective filing date of this application.

Gergiou (5,866,344), which was previously applied in the non-final office action sent on 3/10/2005, is now re-applied since Georgiou has an earlier date than the effective filing date of this application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Pensee T. Do/
Examiner, Art Unit 1641
/Jacob Cheu/
Primary Examiner, Art Unit 1641